DATA EVALUATION RECORD
Ethaboxam (LGC-30473)
PC Code: 090205
TXR#: 0056241
MRID#: 48535645

Study Type: 28-Day Dermal Toxicity - Rat;
OPPTS 870.3200

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
One Potomac Yard
2777 S. Crystal Drive
Arlington, VA 22202

Prepared by

Tetrahedron Incorporated
1414 Key Highway, Suite B
Baltimore, MD 21230

Principal Reviewer: _____ Date: 4/13/2012
Henry Spencer, Ph.D.

Secondary Reviewer: _____ Date: 4/16/2012
William Burnam, M.S.

Quality Assurance: _____ Date: 4/18/2012
Nasrin Begum, Ph.D.

Contract Number: EP-W-10013
Work Assignment No.: WA-0-01

Task Number: 1-1-86
EPA Reviewer//WAM: Christina Swartz and Karlyn Middleton// Kit Farwell and Lori Brunsman

Disclaimer

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EPA Reviewer: Karlyn Middleton **Signature:**
Risk Assessment Branch 2, Health Effects Division (7509P) **Date:**
EPA Work Assignment Manager: Lori Brunsman **Signature:**
Sci. Info Mgmt. Branch, Health Effects Division (7509P) **Date:**

Template version 09/11

TXR#: 0056241

DATA EVALUATION RECORD

STUDY TYPE: 28-Day Dermal Toxicity -Rat; OPPTS 870.3200 [§82-2] (rodent); OECD 410.

PC CODE: 090205 **DP BARCODE:** D399440

TEST MATERIAL (PURITY): LGC-30473(Ethaboxam) a.i. 97.5%

SYNONYMS: None presented

CITATION: Author: Higgs, P. (2003)LGC-30473: Twenty-Eight Day Dermal Toxicity Study in the Rat, Amended report. Huntingdon Life Sciences, Cambridgeshire PE28 4HS England. Laboratory report: LFK 34/963103,July 30, 2003. MRID 48535645. Unpublished

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EXECUTIVE SUMMARY: In a 28-day dermal toxicity study (MRID48535645), Ethaboxam 97.5% a.i, (batch no.: 4-1) was applied to the shaved skin of 5 rats of the Sprague-Dawley [(Crl: CD) BR VAF PLUS strain]/sex/dose at dose levels of 0, 100, 300, or 1000 mg/kg bw/day, 6 hours/day for 5 days/week during a 28-day period.

There were no compound related effects on mortality, clinical signs, chemistry, or organ weights. Food intake was variable in both sexes but not considered toxicologically significant. There were shortened APTT values in 2 females at 1000 mg/kg bw/day, but the changes were not accompanied by changes in hematology or histopathology. There was dermal irritation reported at 300 and 1000 mg/kg bw/day in males and delineated by microscopic examination. There were decreased body weights and body weight gains in males at 1000 mg/kg bw/day.

The systemic toxicity LOAEL is 1000 mg/kg bw/day in male rats, based on decreased body weight and weight gains without a significant loss of food intake. The NOAEL is 300 mg/kg bw/day.

The LOAEL for dermal irritation is 300 mg/kg bw/day in male rats based on histopathological changes of epithelial hyperplasia, hyperkeratosis, scabbing and dermal inflammation. The NOAEL is 100 mg/kg bw/day.

This 28-day dermal toxicity study in the rat is acceptable, *non-guideline* and satisfies the guideline requirement for a 28-day dermal toxicity study (OPPTS 870. 3200; OECD 410) in rat. This study was completed earlier than the 1998 guidelines and used only 5 animals per sex per dose while the guidelines now call for the use of 10 per sex per dose.

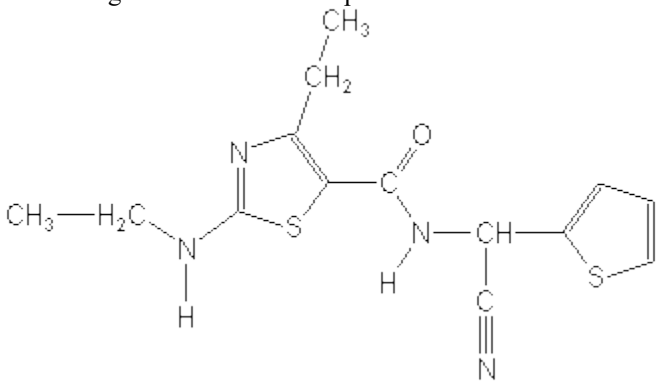
COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were) provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: LGC-30473

Description:	White crystalline powder (at analysis 1996 in Korea): light brown powder as received and analyzed in 1997 in England and reported in study report. Stability: stated as 8 days under the stated storage conditions of 4℃in the dark.
Lot/batch #:	4-1
Purity:	97. 5% a. i.
Compound stability:	Stable for 8 days at 4℃or for 2 days at ambient conditions
CAS #:	*Not available*
Structure:	Note: Image obtained from wikipedia.com



2. Vehicle and/or positive control: 1% methylcellulose

3. Test animals:

Species:	Rat	
Strain:	Sprague-Dawley(Crl: CD BR® VAF PLUS™)	
Age/weight at study initiation:	55 days, 198-222 g males and 163-190 g, females.	
Source:	Charles River UK Ltd, Margate , Kent, England	
Housing:	Individually, in metal cages with wire mesh flooring	
Diet:	Standard pelleted rodent diet (Special Diet Services Rat and Mouse Maintenance Diet), *ad libitum*	
Water:	analyzed source provided, *ad libitum*	
Environmental conditions:	**Temperature:**	17-25 ℃
	Humidity:	40-78%
	Air changes:	Not provided
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	9 days	

B. STUDY DESIGN:

1. In life dates: Start: August 9, 1996; End: September 5, 1996

2. Animal assignment: Animals were assigned by a computer generated list for random allocation based on producing similar weights within each group to the test groups noted in Table 1.

TABLE 1: Study design:

Test group	Dose (mg/kg bw/day)	# Male	# Female
Control	0	5	5
Low	100	5	5
Mid	300	5	5
High	1000	5	5

3. **Dose selection rationale:** This study was a preliminary toxicity study and the dose levels were selected based on the use of a high dose level as the limiting dose and the lower doses of 300 and 100 mg/kg/day were relative to EEC labeling requirements. This sequence was the same as was used in a preliminary 7-day dermal toxicity study performed at this laboratory (Report No. LKY 33/960965). Results from this 7-day previous study were not reported here.

4. **Concentrations in test Formulations:** Weekly during the study, the formulations were sampled and stored frozen for analysis. Only 1 sample time analysis was reported.

TABLE 2: Concentrations of LGC-30473 in Test Formulations:

Date of formulation	Group	Nominal conc. (mg/ml)		Analyzed conc. (mg a. i. /ml)			RME (%)
		m.a.s.	a.i.	Analysis 1	Analysis 2	Mean	
Aug 8, 1996	Control	0	0	ND	ND	ND	-
	2	25	24.4	23.1	24.3	23.7	-2.9
	3	75	73.1	71.2	72.5	71.9	-1.6
	4	250	244	241	243	242	-0.8

ND None detected (<0.08 mg/ml)
RME Relative Mean Error, representing the deviation from nominal a. i.
m. a. s. Material as supplied
a. i. Active ingredient

The formulations as sampled were adequate. Stability and the verification of the analytic procedure were presented previously in LKY 35/961328.

5. **Preparation and treatment of animal skin:** Approximately 24 hours before the first application and as needed thereafter, the fur of each test animal was clipped and shaved from the dorsal area of the trunk over an area of at least 10% of the body surface. The skins were not abraded. The applied quantities of the test substance were adjusted weekly to individual animal body weight. The test substance/vehicle suspension was evenly dispersed over the prepared skin. And covered with impervious bandage consisting of cause covered with 'Elastoplast' elastic adhesive dressing backed with impervious "Sleek". The dressings were removed after 6 hours and the application areas were cleaned with warm (30-40℃) water and gently blotted dry.

Rats in the control group were exposed to the 1% CMC vehicle using the same procedure as described for the treated rats.

The test substance formulations were mixed by inversion and were then mixed by a magnetic stirrer for at least 10 minutes before dosing.

5. **Statistics:** "All statistical analyses were carried out separately for males and females using

the individual animal as the basic experimental unit.

The following sequence of statistical tests was used for bodyweight gains, cumulative food consumption, organ weight, and clinical pathology data.

If the data consisted predominantly of one particular value (relative frequency of the mode exceeds 75%), the proportion of values different from the mode were analyzed by Fisher's exact test (Fisher 1950). Otherwise: Bartlett's test (Bartlett 1937) was applied to test for heterogeneity of variance between treatments. If significant heterogeneity was found at the 1% level, a logarithmic transformation was tried to see if a more stable variance structure could be obtained.

If no significant heterogeneity was detected (or if a satisfactory transformation was found), a one-way analysis of variance was carried out followed by Williams' test (Williams 1971/2) for a dose related response.

If significant heterogeneity of variance was present and could not be removed by a logarithmic transformation, the Kruskal-Wallis analysis of ranks (Kruskal & Wallis 1952/3) was used. This analysis was followed by the non-parametric equivalent of Williams' test (Shirley's test (Shirley 1977).

Covariate analysis of organ weight data (with final bodyweight as covariate) was also performed using adjusted weights for organs here a correlation between organ weight and bodyweight is establishe3d at the 10% level of significance (Angervall & Carlstrom 1963). Additional or alternative statistical methods were used when considered appropriate. Significant differences between control animals and those treated with the test substance are expressed at the 5% (* $p \leq 0.05$) or 1% (** $p \leq 0.01$) level and were supported by a significant analysis of variance. "

The reviewers consider the statistical analyses to be appropriate for the data evaluated.

C. METHODS:

1. Observations:

1a. Cageside observations: Animals were observed daily for signs of ill health, behavioral change, toxicity and the presence of dermal irritation. The animals were examined for signs of local skin irritation at the same time each day after removing the gauze patches and were evaluated using the Draize method. The exact times of observations were not provided in the report.

1b. Clinical examinations: Clinical examinations were conducted early each working day and again in the late afternoon. A similar procedure was followed on Saturdays, Sundays and public holidays excepting that the final observation was made at approximately mid-day. No method of reporting these findings was supplied.

1c. Neurological evaluations: These type evaluations (measurements) were not performed in this study. These type evaluations would be available from more extensive studies performed later since this was a "preliminary" toxicity study. The

use of the term "preliminary" has been taken to mean essentially a range finding study by the reviewers.

2. **Body weight:** See Table 5 below. Animals were weighed prior to initiation of the study and at the beginning of each study week.

3. **Food consumption:** See Table 6 below. Food consumption was determined weekly individually from the weight of the offered diet at the beginning of a specific week and its difference to the re-weight amount after several days. Mean food consumption per group was reported as g food/animal/week. Food consumption ratios were calculated weekly.

4. **Ophthalmoscopic examination:** Eyes of all animals were examined macroscopically at termination, but the exact methodology was not provided.

5. **Hematology and clinical chemistry:** After fasting, blood was collected from all animals from the orbital sinus while under light ether anesthesia prior to termination for hematology and clinical chemistry and coagulation studies from all animals. The CHECKED (X) parameters were examined.

   a. **Hematology:**

Table 3: Hematology parameters examined

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc. (MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
	Platelet count*		Reticulocyte count
	Blood clotting measurements*		
X	(Thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time)		

* Recommended for 28-day dermal toxicity studies based on Guideline 870. 3200

b. Clinical chemistry:

Table 4: Clinical chemistry parameters examined

X	ELECTROLYTESX	X	OTHER
X	Calcium	X	Albumin*
X	Chloride	X	Creatinine*
	Magnesium	X	Urea nitrogen*
X	Phosphorus	X	Total Cholesterol*
X	Potassium* (K)	X	Globulins
X	Sodium* (NA)	X	Glucose*
X	**ENZYMES** (more than 2 hepatic enzymes, eg. , *)	X	Total bilirubin
X	Alkaline phosphatase (AP)*	X	Total protein*
	Cholinesterase (ChE)		Triglycerides
	Creatine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)		
X	Alanine aminotransferase (ALT/also SGPT)*		
	Aspartate aminotransferase (AST/also SGOT)*		
	Gamma glutamyltransferase (GGT)*		
	Glutamate dehydrogenase		
	Sorbitol dehydrogenase*		

* Recommended for 28-day dermal toxicity studies based on Guideline 870. 3200

6. **Urinalysis*:** Urine was not collected from these study animals. However, it is optional for 28-day dermal toxicity studies.

7. **Sacrifice and pathology:** All animals were sacrificed on schedule and subjected to gross pathological examination. The CHECKED (X) tissues were collected for histological examination. The (+) organs, in addition, were weighed. Tissues checked XX were required for histopathological examination for groups 1 and 4. Skin (treated and untreated) in all male groups were examined.

Table 5: Organs and Tissues examined

X	DIGESTIVE SYSTEM	X	CARDIOVASC. /HEMAT.	X	NEUROLOGIC
X	Tongue	X	Aorta, thoracic*	X+	Brain*+
X	Salivary glands*	XX	Heart*+	X	Peripheral nerve*
X	Esophagus*	X	Bone marrow*		Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	XX+	Spleen*+	X	Eyes (optic nerve)*
X	Jejunum*	X	Thymus*+	X	GLANDULAR
X	Ileum*			XX+	Adrenal gland*+
X	Cecum*	X	UROGENITAL		Lacrimal gland
X	Colon*	XX+	Kidneys*+	X	Parathyroid*
X	Rectum*	X	Urinary bladder*	X	Thyroid*
XX+	Liver*+	XX+	Testes*+	X	OTHER
	Gall bladder* (not rat)	XX+	Epididymides*+	X	Bone (sternum and/or femur)
	Bile duct* (rat)	X+	Prostate*	X	Skeletal muscle
X	Pancreas*	X+	Seminal vesicles*	X	Skin* (treated & untreated areas)
X	RESPIRATORY	X+	Ovaries*+	X	All gross lesions and masses*
X	Trachea*	X	Uterus*+	X	head
X	Lung*	X	Mammary gland*		
	Nose*	X	Vagina		
X	Pharynx*				
X	Larynx*				

* Recommended for 28-day dermal toxicity studies based on Guideline 870. 3200
+Organ weights required.

II. RESULTS:

A. OBSERVATION(s):

1. **Clinical signs of toxicity:** No adverse clinical signs were reported. Hair loss was observed in every animal at day 10 onward. Additionally, scabbing incidences were seen at the high dose in males and at all doses in females.

2. **Mortality:** All animals survived to the termination point of the study

3. **Neurological evaluations:** Neurological evaluations were not provided in this study.

4. **Dermal Irritation:** There were no instances of erythema or edema observed; however, there were incidences of scabbing and hair loss noted in the study.

B. BODY WEIGHT AND WEIGHT GAIN:

Body weight in males was essentially similar to controls in dose groups up to 300 mg/kg/day. The 1000 mg/kg/day males however, exhibited reductions in weights starting in week 1 (-5%) and worsened through week 4 (-10%). The total weight gains in males were also similar to controls with the exception of a statistically significant reduction of 41% over the length of the study.

Females at 100 mg/kg/day body weight at week 0 was similar to the control group while the 300 and 1000 mg/kg/day groups were 5% and 6% lower than the control. Body weights in the 300 mg/kg/day group gained slightly from week 0, and remained from 8% to 5% less than controls until the end of the study. The total weight gain for the 300 mg/kg/day group was essentially the same as the controls.

The 1000 mg/kg/day female group weight started lower than controls in week 1 (-8%) but gained back to a normal rate by study end. Total study weight gains in the females were essentially normal, but may have been affected in the 1-2 weeks which was overcome later. The increasing weight loss and statistically significant 41% loss of gain in the males is considered adverse because of the increasing loss over time.

TABLE 6. Group mean body weights and body weight gains during 28 days of treatment [a]

Dose rate mg/kg/day	Week 0	Body weights (g±SD) (N=5 per group)				Total weight gain	
		Week 1	Week 2	Week 3	Week 4	G Week 0-4	% of control
Male							
0	310	340.8±20.3	368.2±25.7	393.4±20.7	405.4±20.4	95.4±16.6	-
Low 100	308	341.4±6.4	365.6±5.9	393±11.9	400.4±17.0	92.2±12.4	97
Mid 300	317	346.8±4.1	380±8.9	398.8±7.4	412.2±14.4	94.8±10.9	100
High 1000 &	307 -1%	323.4±23.4 -5%	345.6±34.0 -6%	359±34.5 -9%	363.6±45.6 -10%	56.4±35.2* -41%	59
Female							

Dose rate mg/kg/day	Week 0	Body weights (g±SD) (N=5 per group)				Total weight gain	
		Week 1	Week 2	Week 3	Week 4	G Week 0-4	% of control
0	230	240±18.7	250.2±18.8	260.6±24.8	256.8±26.3	25.4±12.3	-
Low 100	226	235.4±11.5	250.2±11.6	263±13.4	261.2±14.6	35.4±11.4 **+39%	138
Mid 300 **	218 -5%	223.8±2.3 -7%	228.4±8.6 -8%	245±9.6 -6%	243.4±9.9 -5%	25.4±12.3 0%	100
High 1000 **	216 -6%	219.6±13.5 -8%	233.4±16.1 -7%	247.4±20.8 -5%	251±23.5 -2%	34.6±16.0 +36%	135

[a]Data obtained from pages32, 62in the study report.
*Statistically different (p <0. 05) from the control.
Means and SD values were calculated by the reviewers.
**change from control.

C. FOOD CONSUMPTION AND EFFICIENCY:

1. **Food consumption:** Food consumption in the groups was variable, based on the S. D. with only 5 animals in each group. Males at 1000 mg/kg/day in week 2 exhibited a 10% reduction in food intake compared to controls, but rebounded to normal the following 2 weeks of the study.

   Females at 1000 mg/kg/day exhibited an 11% reduction in food intake, but reverted to near normal compared to controls in the later 3 weeks of the study.

TABLE 7. Group food Consumption during28 days of treatment [a]

Dose rate mg/kg/day	Group Mean Food Consumption (g) (N=5 per group)				Total food intake	
	Week 1	Week 2	Week 3	Week 4	g	% of control
Male						
0	214.8±6.3	233±23.0	225±11.5	221.2±10.7	894	-
Low 100	224.2±5.3	218±15.3	218.2±12.2	209.4±16.7	870	97
Mid 300	224.6±6.7	233.8±6.9	227.6±8.6	226±12.2	912	102
High 1000 &	210.2±18.4 -2%	209.2±15.1 -10%	222.2±11.9 -1%	209.4±16.7 -5%	850 -5%	95
Female						
0	159.8±4.1	168.6±21.1	180±23	166.2±22	675	-
Low 100	164.4±4.2	175±11	182.2±10.8	169.8±6.2	691	102
Mid 300 **	150.8±4.1 -6%	158±11.6 -6%	173.6±8.2 -4%	158.4±3.1 -5%	641 -5%	95
High 1000 **	142.4±18.5 -11%	160.2±18.7 -5%	178.4±19.5- -1%	163.6±19.9 -2%	645 -4%	96

[a]Data obtained from pages3, 64, 65in the study report.
Means and SD values calculated by reviewers
**Percent change calculated by reviewers

2. **Food efficiency:** Food efficiency data were not calculated in the report.

D. OPHTHALMOSCOPIC EXAMINATION: There was no ophthalmoscopic examination in this study. There were 2 instances of damaged eyes from blood collections which are considered to be non-treatment related.

E. BLOOD ANALYSES: There were few effects reported in the blood analyses tables in the study.

1. Hematology: The study results reported did not show hematological changes in any male treatment group compared to controls. At 300 and 1000 mg/kg/day females exhibited statistically significant lower lymphocyte values than the controls, however, the values are considered to be normal. The females at 1000 mg/kg/day showed a shortened APTT value which was 12% ($p< 0.05$) lower than the controls. This effect may have been due to exposure to the chemical, but it is not supported by any hematological or histological changes reported in the study which would have activated the clotting mechanism. Additionally, the shortened mean time value is the result of only 2 of 5 animals with lower values than normally seen in this study. This statistical value is not considered to be the result of chemical exposure without further information on the range of normal for this species in this laboratory. The prothrombin times were normal.

2. Clinical chemistry: Clinical chemistry results were for the most part unchanged as compared to controls from treatment, with the exception of slightly ($p<0.05$) increased albumin values in females at all treatment levels as compared to controls. However, there were no histological findings that could be related to any clinical chemistry result and there was no increase related to dosage. The change is considered inconsequential. A second change ($p<0.01$) was noted as a 4% reduction in Ca levels in males at 1000 mg/kg/day. Whether this change is due to treatment is problematical. However, with such small numbers of animals, we would consider the small change to be of no consequence.

F. URINALYSIS: Urinalysis was not done in the study.

G. SACRIFICE AND PATHOLOGY: There were no gross pathological changes reported by the pathologists which were related to treatment. However, there were treatment-related microscopic lesions observed at ≥ 300 mg/kg/day.

1. Organ weight: The organ weights were variable and only the adjusted mean brain weight at 1000 mg/kg/day was statistically significantly greater ($p<0.01$) than controls. This was due to the only slight increase in absolute weight above the controls and the 10% reduction in body weight of that group.

Females in the control group exhibited the greatest variability of liver weights causing a lower value than would be expected. Treated groups were not significantly different from controls when the 2 aberrant control values were accounted for. Other organ weights were not significantly altered from control values.

2. Gross pathology: The gross pathology summary showed only occasional, sporadic incidences of changes that were no worse than those found in controls. Therefore, there were no lesions clearly attributable to treatment.

3. Microscopic pathology: Male rats at 1000 mg/kg/day exhibited liver sinusoidal dilatation or congestion in 3 of 5 animals compared to 1of 5 animals in control. Grading of the liver effects was absent. No other tissues examined had incidences of changes which were more significant than those found in controls with the exception of the treated skin. The males in

the 300 and 1000 mg/kg/day groups each exhibited moderate hyperplasia, minimal hyperkeratosis. Scab, ulcer and dermal inflammation in 1 or 2 animals in each group were reported while there were 0/5 animals affected in the control and 100 mg/kg/day group. Effects considered to be related to exposure are limited to 300 and 1000 mg/kg/day in male rats. There were no effects reported in females which were considered to be treatment related.

Table 8. Microscopic Findings in Treated Skin and Liver

	Males			
	0	**100**	**300**	**1000**
NUMBER EXAMINED	**5**	**5**	**5**	**5**
Epithelia Hyperplasia Total Trace Minimal Moderate	 2 0 2 0	 1 1 0 0	 3 0 3 0	 4 1 1 2
Hyperkeratosis minimal	 0	 0	 2	 1
Dermal Inflammation	0	0	1	1
Scab	0	0	1	2
Ulcer	0	0	0	2
Liver-sinusoidal dilatation/congestion	 1	 0	 0	 3

III. DISCUSSION AND CONCLUSIONS:

A. <u>INVESTIGATORS' CONCLUSIONS</u>: The investigators stated that 28 days of dermal exposure to LGC-30473 was associated with systemic toxicity at 300 and 1000 mg/kg/day. They noted that reduced food consumption and retarded bodyweight gain were seen in both sexes early in the study at 1000 mg/kg/day and in females only at 300 mg/kg/day. Microscopic evaluations found treated skin with epithelial hyperplasia, hyperkeratosis. Ulceration was also seen in males at 1000 mg/kg/day.

At 1000 mg/kg/day 2 females exhibited shortened APTT times which were statistically significant. Variations in hematology and blood chemistry values were seen as spurious significant findings without dosage relationship and lack of pathological changes.

The investigators noted that 100 mg/kg/day was a NOEL for rats following 28 days of dermal exposure to LGC-30473.

B. <u>REVIEWER COMMENTS</u>: After reviewing the data, it is concluded that the systemic LOAEL is established at 1000 mg/kg/day in male rats, based on the decreased body weights and weight gains ($p<0.05$). The systemic NOAEL is 300 mg/kg/day.

There were no biochemical or hematological changes other than the statistically significant shortened APPT times ($p<0.05$) which were overtly chemically related.

Dermally, the LOAEL is 300 mg/kg/day based on the epithelial hyperplasia, hyperkeratosis, scabbing, ulceration and inflammation reported in the microscopic incidence summary. The NOAEL is 100 mg/kg/day in males.

The reviewers do not agree with the use of food consumption as an indicator of toxicity in this study. The 11% drop of food intake in females at week 1 of the study does not necessarily show toxicity, but more likely the handling effects in the study. Further exposure doses not worsen the food intake situation. The only toxicity that may be related to intake is the slight dilatation of the liver sinusoidal dilatation and the increasing loss of weight and weight gains reported in the males at 1000 mg/kg/day. Decreasing body weights indicate that the chemical is absorbed through the skin in the study.

Perusing the weights at week 0 in individual females at 300 and 1000 mg/kg/day indicated that several animals were small and tended to skew the starting weights and gains lower, suggesting a chemical effect. However, the gains per group per week were essentially the same as the control gains and are not considered an effect.

C. STUDY DEFICIENCIES:

This study was completed earlier than the 1998 guidelines and used only 5 animals per sex per dose while the guidelines now call for the use of 10 per sex per dose.